PROCESS FOR CATALYZING THE OXIDATION OF ORGANIC COMPOUNDS

ABSTRACT

Oxidation of organic compounds is catalyzed by addition of a catalytic amount of a metalloporphyrin in a non-reactive aprotic solvent.

FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)
A0000135-01-CFP	10/049208

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/07726	09 August 2000	10 August 1999

TITLE OF INVENTION
PROCESS FOR CATALYZING THE OXIDATION OF ORGANIC COMPOUNDS

APPLICANT(S) FOR DO/EO/US
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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto. (FILED IN ENGLISH)
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☒ are attached hereto (required only if not communicated by the International Bureau). (ANNEX TO IPER)
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Published Specification, WO 01/10797

EXPRESS MAIL NO. EF378134476US

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/049208	PCT/EP00/07726	A0000135-01-CFP

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☒	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1040.00
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$890.00
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$740.00
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$710.00
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =	$1,040.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$0.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	18 - 20 =	0	x $18.00	$0.00	
Independent claims	1 - 3 =	0	x $84.00	$0.00	
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00	

TOTAL OF ABOVE CALCULATIONS =	$1,040.00	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.	$0.00	
SUBTOTAL =	$1,040.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +	$0.00	
TOTAL NATIONAL FEE =	$1,040.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐	$0.00	
TOTAL FEES ENCLOSED =	$1,040.00	
Amount to be: refunded	$	
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a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **23-0455** in the amount of **$1,040.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **23-0455** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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8 February 2002
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PROCESS FOR CATALYZING THE OXIDATION OF ORGANIC COMPOUNDS

FIELD OF THE INVENTION

The study of drug metabolism is an important part of the very expensive drug R&D process. In humans and other mammals, many drugs are metabolized through oxidative reactions catalyzed by heme- and cytochrome-containing enzymes. Cytochrome P450 mono-oxygenases, the main enzymes involved in drug oxidative metabolism, have in their active site a heme moiety.

Synthetic metalloporphyrins can serve favorably to mimic oxidative catalytic reactions occurring in biological systems, with the aim of producing and identifying oxidative products of drug candidates, in quantities allowing in vivo studies.

PCT application WO 96/08455 discloses a process for the preparation of oxidative products using various combinations of a synthetic metalloporphyrin, a co-oxidizing reagent, and a solvent. The solvent is generally a CH_3CN/CH_2Cl_2 combination. One of the major inconveniences of processes of this type is the fact that they frequently provide incomplete yields of the sought-after individual products as well as low conversion percentages. As a result, they can rarely be used in a reliable fashion in integrated discovery processes. In fact, their use is generally limited to experimental validation.

SUMMARY OF THE INVENTION

In accordance with the present invention, the inventor has unexpectedly found that the yields of oxidative reactions involving metalloporphyrins and which can be useful for the synthesis of metabolites of organic compounds of interest could be increased in a substantial manner through the use of an inert aprotic solvent.

Thus, one of the objects of the present invention is a process for the oxidation of organic compounds. This process comprises reacting the selected organic compound with catalytic amounts of a metalloporphyrin and of an oxidizing agent in the presence of an inert aprotic solvent and recovering the desired products obtained therefrom.

The process of the invention is extremely useful in pharmaceutical research and development as it can be used to perform preliminary evaluations of the metabolic processes which are likely to occur when a given compound is tested in vivo. These preliminary evaluations can be performed rapidly without having to carry out expensive and time consuming in vivo experiments. Furthermore, the process of the present invention provides better yields of individual products than those obtained using prior art processes. In other words, the process of the present invention opens the possibility of obtaining and analyzing in a more systematic fashion a higher number of individual potential metabolites for a given selected compound on which the process is carried out.

DETAILED DESCRIPTION OF THE INVENTION

The present invention therefore concerns a process for the efficient oxidative preparation of metabolites of organic compounds. The invention comprises reacting an organic compound of interest with a catalytic amount of a metalloporphyrin and an oxidizing agent, in a non-reactive aprotic solvent.

As mentioned previously, several drugs are metabolized through oxidative reactions. The process of the instant invention is therefore applied favorably to organic compounds of interest possessing one or several functional groups which will react to oxidation conditions. Some of these functional groups are described below but as the skilled person will readily appreciate, the list provided is not intended to be exhaustive. In fact, the process of the invention can be used on any organic compound which can be oxidized in some way by enzymes involved in drug oxidative metabolism.

Preferably, compounds containing heteroatoms, such as nitrogen or sulfur, can be efficiently oxidized through the process of the invention, particularly to a higher oxidation state, and more particularly to their highest oxidation state. For example, primary amines can be readily converted to their corresponding hydroxylamines, nitroso- or nitro- derivatives; and tertiary amines to their corresponding *N*-oxides.

Also, C-H bonds can be conveniently hydroxylated into C-OH bonds by metalloporphyrin-catalyzed oxidations according to this invention. Examples include labile C-H bonds, such as those in benzylic positions or C-H bonds wherein the carbon atom is adjacent to a heteroatom (e.g. N, S, O, or the like). Those are particularly reactive to these conditions.

In this manner, primary alcohols can be converted to their corresponding aldehydes; in turn aldehydes can be converted to their corresponding acids, and said acids may further undergo decarboxylation.

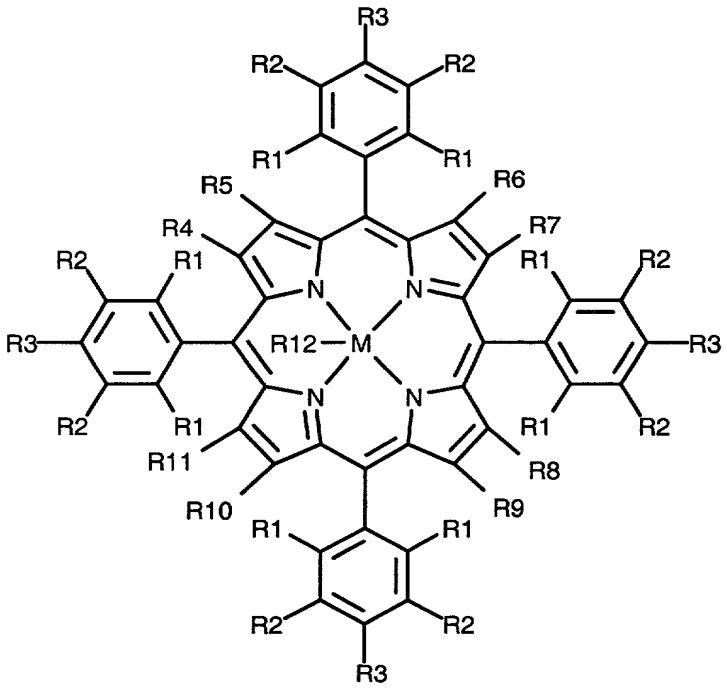
Through the process of the invention, secondary alcohols can be converted to their corresponding ketones.

Carbon-carbon double bonds can be epoxidized by metalloporphyrin-catalyzed oxidation according to this invention, and aromatic groups can be oxidized into corresponding phenols or quinones.

The main parameters involved in the process of the invention are the starting material which is usually an organic compound of interest, the reactants which usually include a metalloporphyrin, an oxidizing agent and an inert aprotic solvent, and the reaction conditions which comprise the reaction temperature and the reaction time. Each of these parameters will be discussed in further detail below.

Metalloporphyrins

Synthetic metalloporphyrins are described in international patent application WO 96/08455. The term "metalloporphyrin", as used herein, refers to porphyrin compounds of formula (I):



wherein:

R1, R2 and R3 independently represent hydrogen or an electron-withdrawing group

such as Cl, F, Br, SO_3Na, or the like,

R4, R5, R6, R7, R8, R9, R10 and R11 independently represent hydrogen or an electron-withdrawing group such as Cl, F, Br, NO_2, CN, SO_3Na or the like,

R12 is Cl, acetate or the like,

M is selected from the group consisting of iron, manganese, chromium, ruthenium, cobalt, copper and nickel.

Preferred metalloporphyrins include tetrakis(pentafluoro-phenyl)porphyrin Mn(III) chloride, herein abbreviated as Mn(TPFPP)Cl, which is the compound of formula (I) above wherein M is manganese, R1, R2 and R3 are fluorine, R4, R5, R6, R7, R8, R9, R10 and R11 are hydrogen, and R12 is chlorine.

Preferred metalloporphyrins also include:

tetrakis(pentafluoro-phenyl)porphyrin Fe chloride, abbreviated as Fe(TPFPP)Cl, which is the compound of formula (I) above wherein M is iron, R1, R2 and R3 are fluorine, R4, R5, R6, R7, R8, R9, R10 and R11 are hydrogen, and R12 is chlorine;

tetrakis(2,6-dichlorophenyl)porphyrin Mn chloride, abbreviated as Mn(TDCPP)Cl, which is the compound of formula (I) above wherein M is manganese, R1 is chloride, R2, R3, R4, R5, R6, R7, R8, R9, R10 and R11 are hydrogen, and R12 is chlorine;

tetrakis(2,6-dichlorophenyl)porphyrin Fe chloride, abbreviated as Fe(TDCPP)Cl, which is the compound of formula (I) above wherein M is iron, R1 is chloride, R2, R3, R4, R5, R6, R7, R8, R9, R10 and R11 are hydrogen, and R12 is chlorine;

tetrakis(2,6-dichlorophenyl)-octachloroporphyrin chloride Fe, abbreviated as $Fe(TDCPCl_8P)Cl$, which is the compound of formula (I) above wherein M is iron, R1 is chloride, R2 and R3 are hydrogen, R4, R5, R6, R7, R8, R9, R10 and R11 are chloride, and R12 is chlorine;

the compound $Mn((Cl_2Ph)_4 (NO_2)P)Cl$, of formula (I) above wherein M is manganese, R1 is chloride, R4 is NO2, R2, R3, R5, R6, R7, R8, R9, R10, and R11 are hydrogen, and R12 is chlorine;

the compound $Mn((Cl_2Ph)_4(NO_2)_2P)Cl$, of formula (I) above wherein M is manganese, R1 is chloride, R5 and R6 are NO_2, R2, R3, R4, R7, R8, R9, R10 and R11 are hydrogen, and R12 is chlorine.

The amount of the metalloporphyrin catalyst usually ranges between 0.5 and 10 % molar and is preferably about 1 % molar.

Oxidizing agents

Various oxidizing agents can be used in the instant invention. It should be noted that the very nature of the oxidizing agent does not appear to be a limiting factor in the process of the present invention. The person skilled in the art can thus select the appropriate oxidizing agent among the wide variety of compounds which have been used in metalloporphyrin-catalyzed oxidative reactions. A list of possible agents includes, but is not limited to: iodosylbenzene, also known as iodosobenzene, aqueous solutions of hydrogen peroxide (concentration about 30 to 45 %), anhydrous equivalents of hydrogen peroxide such as sodium percarbonate, urea hydrogen peroxide complex or the like, potassium monopersulfate, sodium hypochlorite, *tert*-butyl hydroperoxide, cumene hydroperoxide, *m*-chloroperbenzoic acid, and magnesium monoperoxyphthalate. Preferred oxidants include iodosylbenzene, any source of hydrogen peroxide, and potassium monopersulfate.

Oxidation using hydrogen peroxide is more efficient in the presence of a co-catalyst such as imidazole, ammonium acetate, *N*-hexylimidazole, amine *N*-oxides, tetrabutylammonium acetate, *tert*-butyl pyridine, pyridine, 4-methylpyridine, and 2,4,6-trimethyl-pyridine. For a review, see "State of the art in the development of biomimetic oxidation catalysts" Rocha Gonsalves, A.M.; Pereira, M.M. *J. Mol. Catal. A: Chem.* **1996**, *113*, 209.

Solvent

The metalloporphyrin-catalyzed oxidation of the invention is performed in an inert solvent, which in fact can contain one or several solvents. The term 'inert aprotic solvent', when used herein, is intended to designate any solvent or any mixture of solvents which, when evaluated in a global manner, does not react in any substantial fashion with the starting materials or with the products of the reaction. More particularly, the solvent should not react with the oxidizing agent. Furthermore, the solvent should be resistant to hydrogen abstraction.

In the case of a mixture of solvents, this mixture usually contains a so-called "main solvent" and a "co-solvent". It should be noted however that several solvents having similar properties could be used to form the main solvent. Similar considerations apply to an eventual mixture of co-solvents.

The main solvent is present in larger amounts in the solvent mixture than the co-solvent. In fact, it is the main solvent that confers its overall properties to the global solvent mixture, which will then play a key role in the process of the invention. The main solvent should therefore be inert and aprotic.

To the extent possible, the main solvent should have the capability to dissolve the starting material (i.e. the organic compound of interest) and the metalloporphyrin.

Examples of the main solvent include, but are not limited to polyhalogenated aliphatic solvents such as 1,1,2-trichloro-1,2,2-trifluoroethane and the like or polyhalogenated aromatic solvents such as 1,2-dichlorobenzene, 1,2,4-trichlorobenzene, pentafluorobenzene and the like. Preferred polyhalogenated solvents include polyfluorinated aromatic compounds, such as trifluorotoluene (also known as benzotrifluoride) and the like. Trifluorotoluene is a most preferred solvent, which combines the capacity of dissolving a wide variety of organic compounds with a low reactivity towards oxidative conditions.

Although the skilled person can determine by routine experiments the optimal amount of main solvent to be used in each individual case, suitable concentrations of starting material in the chosen solvent can vary between 0.1 M and 0.5 M, preferably 0.1 M.

The co-solvent is present in small amounts in the mixture and is introduced to provide additional properties of interest to the overall solvent mixture, which will be useful at some point but which will not interfere in a significant manner with the reaction itself.

In a first embodiment of the process of the present invention, if any of the organic compound of interest or the oxidizing agent is not soluble in the main solvent, a co-solvent can be used to improve its solubility in the reaction medium.

For example, if the starting material is not soluble in trifluorotoluene or in any main solvent available, a co-solvent can be used in order to improve its solubility in the reaction medium. Preferred co-solvents include highly polar and poorly nucleophilic co-solvents. Preferably, the properties of the co-solvent should be chosen in order to minimize complex formation with the metalloporphyrin. 2,2,2-Trifluoroethanol and, particularly, 1,1,1,3,3,3-hexafluoro-propan-2-ol (also called hexafluoroisopropanol or HFIP) are representative examples of co-solvents that can be used in the process of this invention. More particularly,

hexafluoroisopropanol, can be useful in oxidation reactions performed with iodosylbenzene in one of the organic solvents mentioned above since this co-solvent helps dissolve this particular oxidant in the reaction medium.

The amount of co-solvent used to dissolve the starting material or the oxidizing agent and eventually the catalyst should be kept to relatively low levels with respect to the main solvent. Although the skilled person can determine by routine experiments the optimal amount of co-solvent to be used in each individual case, suitable concentrations can vary between 1 and 30%, preferably between 1 and 20% and more preferably between 1 and 10% with respect with the main solvent.

In a second embodiment of the process of the present invention, the co-solvent can be used in order to facilitate transfer of reactants within the reaction medium. For instance, a co-solvent is used in the case where the starting material or one or several reactants leads to a reaction mixture which comprises a biphasic solution.

For example, in the case where the oxidant is used as an aqueous solution, the reaction is biphasic and a water-miscible co-solvent can be used to facilitate the transfer of the oxidant in the organic phase. A minimal amount of co-solvent, such as hexafluoroisopropanol, is preferred. This co-solvent is miscible with water and it can facilitate dissolution of the starting material.

The amount of co-solvent which should be used in this second embodiment, as expressed in catalytic amounts, usually ranges between 0.25 and 1 equivalent, preferably between 0.3 and 0.5 and is more preferably about 0.4 equivalent with respect to the starting material.

As an alternative to this second embodiment of the invention, a phase-transfer catalyst can be used to facilitate the transfer of any of the reactants into the phase where the reaction will take place. For instance, when the oxidant is used as an aqueous solution, a phase-transfer catalyst can be used to facilitate the transfer of the oxidant in the organic phase.

Examples of phase-transfer catalysts include tetraalkyl ammonium salts (such as dodecyl-trimethyl-ammonium bromide and the like). The amount of phase-transfer catalyst which should be used in this second embodiment, as expressed in catalytic amounts, usually ranges

between 0.05 and 0.5 equivalent and is more preferably about 0.10 equivalent with respect to the starting material.

Temperature and duration of the reaction

The reaction is carried out at a temperature between about -20 °C and 100 °C, and preferably between about -10 °C and 40 °C.

The skilled person should note however that sonication can be used to increase the reaction rate. The reaction is then preferably performed in an ultrasound bath cooled to 0°C.

Generally, the duration of the reaction varies from a few minutes up to 2 h. Advancement can be monitored with TLC or HPLC analytical techniques; thus the reaction is stopped when the oxidation reaction reaches a plateau point beyond which no substantial conversion is observed.

EXAMPLES

Without limiting the invention, the following examples illustrate the implementation of the processes of the invention.

The purity, identity and physico-chemical characteristics of the products prepared are determined as follows:

- the purity is verified by analytical reverse-phase HPLC on a Merck Lachrom apparatus and the Rf observed is given for the eluent used;
- the identity of the products obtained with the proposed structures is verified by their proton nuclear magnetic resonance spectrum and by mass spectrometry.

The ^1H NMR spectra are recorded at 400 MHz on a Brüker instrument, the compounds being dissolved in deuterochloroform with tetramethylsilane as internal standard. The nature of the signals, their chemical shifts in ppm, the number of protons they represent and their exchange capacity with D_2O are noted.

The mass spectra are recorded on a Micromass Platform LC spectrometer (simple quadrupole with positive ionization electrospray). The infrared spectra are recorded on a Nicolet spectrometer.

The phrase "flash chromatography on a silica column" means a method adapted from that of

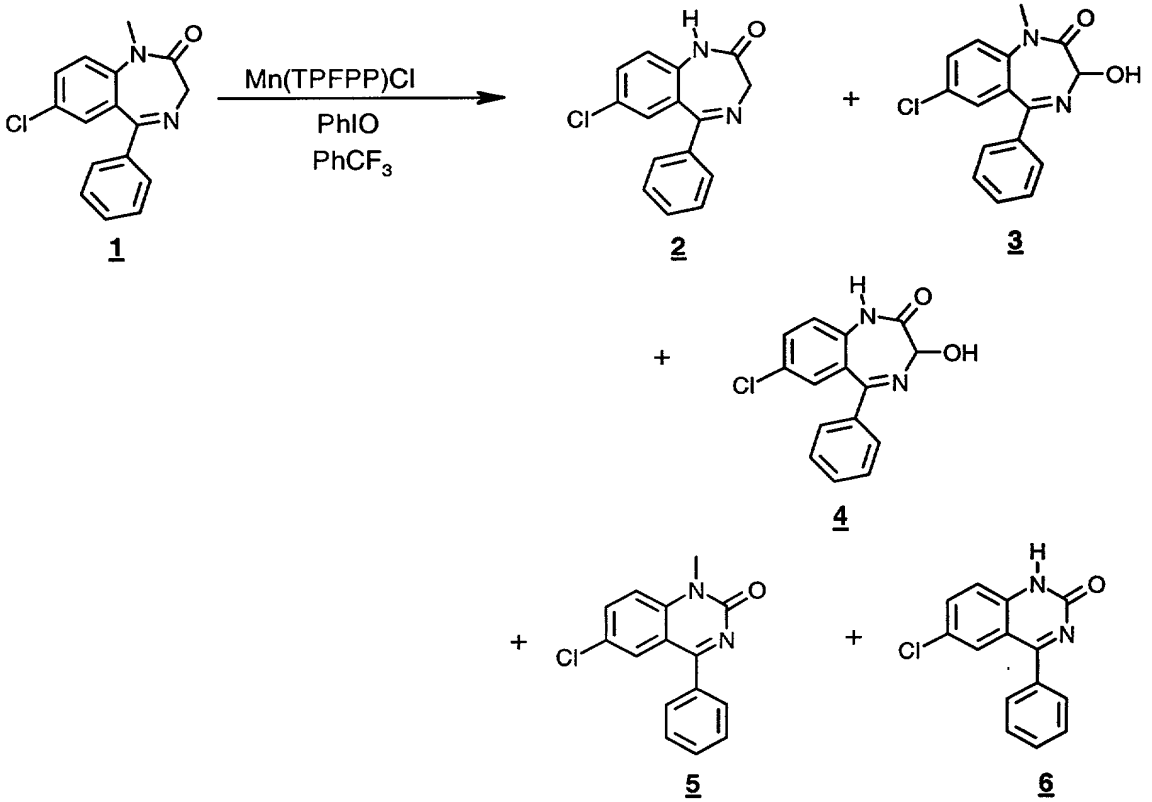
Still *et al.* (1978) J. Org. Chem. 43: 2923. The purity of elution fractions is verified before they are gathered and evaporated.

The terms "evaporation", "elimination" or "concentration" of the solvents mean, possibly after desiccation on an appropriate dehydrating agent such as Na_2SO_4 or $MgSO_4$, a distillation under a pressure of 25 to 50 mm Hg (3,3 to 6,7 kPa) with moderate heating in a water bath at a temperature below 30 °C.

EXAMPLE 1

Oxidation of diazepam (1) with iodosylbenzene (PhIO) catalyzed by tetrakis(pentafluorophenyl)porphyrin manganese (III) chloride in trifluorotoluene.

During this reaction, nordiazepam (**2**), temazepam (**3**), oxazepam (**4**), 6-chloro-4-phenyl-1-methyl-2-(1*H*)-quinazolinone (**5**) and 6-chloro-4-phenyl-2-(1*H*)-quinazolinone (**6**) are formed.



To 240 □L of a solution containing 25 □mol of diazepam (**1**) in trifluorotoluene is added 10 □L of a 25 mM solution of 5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphyrin

manganese (III) chloride (0.25 □mol, 1 mol%) in trifluorotoluene. To the resulting stirring solution is added 3 times a portion of iodosylbenzene (3x5.5 mg, 3x25 □mol, 3 equiv.), one every hour. The reaction is monitored by analytical HPLC one hour after each addition: a sample, prepared with 5 □L of crude and 100 □L of a 5 mM methanolic solution of acetophenone (internal standard) diluted with 395 □L of methanol, is injected into a Nucleosil 5C18 150x4.6 mm column eluting with 50/50 methanol/water at 1 mL/min during 45 minutes. Nordiazepam (**2**), temazepam (**3**), oxazepam (**4**) formed are identified by comparison with authentic samples (Sigma). Their retention times are respectively 21.9, 16.7 and 13.3 min. 6-Chloro-1-methyl-4-phenyl-1*H*-quinazolin-2-one (**5**) and 6-chloro-4-phenyl-1*H*-quinazolin-2-one (**6**), respectively eluting at 25.1 and 20.5 min, are identified in a separate run by isolation and comparison of ^{1}H NMR and MS data with Felix *et al* (1968) *J. Heterocycl. Chem.* 5, 731 and Sulkowski *et al* (1962) *J. Org. Chem.* 27, 4424.

Yields of products from the reaction are shown in the following table:

PhIO	Products obtained: Yield (%)					
(equiv.)	**1**	**2**	**3**	**4**	**5**	**6**
1	31	19	12	3	4	0
2	5	17	6	7	11	4
3	1	9	2	5	10	3

Results form the reaction performed in 1:1 CH_2Cl_2/CH_3CN, solvent conditions representative of the state of the art, are shown below:

PhIO	Products obtained: Yield (%)		
(equiv.)	**1**	**2**	**3**
1	86	1	1
2	83	1	2
3	79	1	2

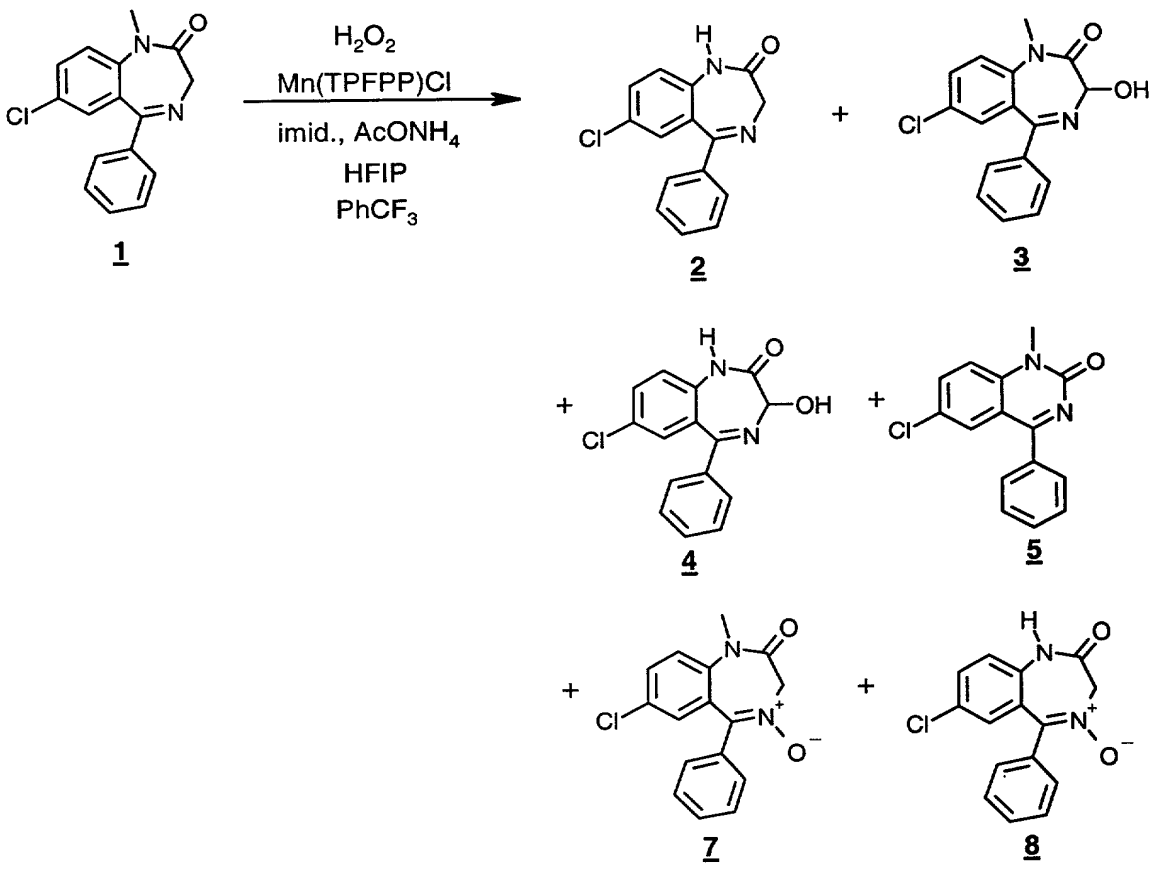
Comparison of both sets of results implies that the use of a solvent such as trifluorotoluene instead of the classical dichloromethane/acetonitrile leads to better diazepam conversion, and formation of a higher number of products in significantly better yields.

EXAMPLE 2:

Oxidation of diazepam (1) with a 30% aqueous solution of hydrogen peroxide catalyzed by tetrakis(pentafluorophenyl)porphyrin manganese (III) chloride in trifluorotoluene

This reaction is more efficient in the presence of catalytic amounts of imidazole (Battioni *et al* (1988) *J. Am. Chem. Soc.* 110, 8462) and ammonium acetate (Thellend *et al* (1994) *J. Chem. Soc., Chem. Comm.*, 1035).

During this reaction, nordiazepam (**2**), temazepam (**3**), oxazepam (**4**), 6-chloro-4-phenyl-1-methyl-2-(1*H*)-quinazolinone (**5**), diazepam *N*-oxide (**7**) and nordiazepam *N*-oxide (**8**) are formed.



To 240 □L of a solution containing 25 □mol of diazepam (**1**) in trifluorotoluene is added 10 □L of a 25 mM solution of 5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphyrin manganese (III) chloride (0.25 □mol, 1 mol%) and 1,1,1,3,3,3-hexafluoro-2-propanol (1.1

□L, 10.4 □mol, 0.4 equiv.) in trifluorotoluene. To the resulting stirring solution is added dropwise an aqueous solution of 30% hydrogen peroxide (2.6 □L, 25 □mol, 1 equiv.), imidazole (6.5 □L of a 1 M aqueous solution, 6.5 □mol, 0.25 equiv.) and ammonium acetate (25 □L of a 1 M aqueous solution, 25 □mol, 1 equiv.) over two hours. Thirty minutes after the addition, the reaction is monitored by analytical HPLC in the same manner as in Example 1. One equivalent of 30% aqueous hydrogen peroxide (2.6 □L, 25 □mol, 1 equiv.) is then added every 10 minutes until 15 equivalents of oxidant are used. The reaction is monitored after the addition of 2, 5, 10 and 15 equiv. of hydrogen peroxide. Diazepam *N*-oxide (**7**) (retention time 8.4 min) and nordiazepam *N*-oxide (**8**) (6.7 min) are identified by comparison with samples prepared from the reaction of diazepam and nordiazepam with *m*-chloroperbenzoic acid (*cf.* Ebel *et al* (1979) *Arzneim.-Forsch.* 29, 1317).

Yields of products from the reaction are shown in the following table:

H_2O_2	Products obtained: Yield (%)						
(equiv.)	**1**	**2**	**3**	**4**	**5**	**7**	**8**
1	71	4	7	0	1	5	0
2	58	8	10	1	1	9	1
5	41	10	13	1	3	10	1
10	26	10	12	2	5	8	2
15	19	10	14	2	8	6	2

Results form the analogous reaction performed in 1:1 CH_2Cl_2/CH_3CN, instead of trifluorotoluene and hexafluoroisopropanol as co-solvent, are shown below:

H_2O_2	Products obtained: Yield (%)			
(equiv.)	**1**	**2**	**3**	**7**
1	84	1	1	2
2	77	2	1	3
5	74	5	3	6
10	74	6	7	7
15	74	5	9	7

When the oxidation is performed with hydrogen peroxide in a biphasic system, better diazepam conversion and yields in products are obtained with trifluorotoluene in the presence of hexafluoroisopropanol in place of the dichloromethane/acetonitrile solvent

system.

Preliminary results from additional experiments currently underway confirm the efficacy of the process of the invention for the oxidation of compounds with relatively different structural parameters.

CLAIMS

1) A process for the oxidation of an organic compound, said process comprising reacting the organic compound to be oxidized with a reaction medium comprising a metalloporphyrin and an oxidizing agent in an inert aprotic solvent selected from a polyhalogenated aliphatic or aromatic solvent,and recovering and identifying the desired reaction products,
with the proviso that the inert aprotic solvent is not dichloromethane, dichloroethane or trichloroethane.

2) Process according to claim 1, wherein the inert aprotic solvent is a polyhalogenated aromatic solvent.

3) Process according to claim 2, wherein the solvent is trifluorotoluene.

4) Process according to claim 1, wherein said reaction medium comprises an inert aprotic main solvent and a co-solvent capable of increasing the solubility of the organic compound in the reaction medium.

5) Process according to claim 4, wherein said co-solvent is a polar and poorly nucleophilic solvent.

6) Process according to claim 5, wherein said solvent is 2,2,2-trifluoroethanol or 1,1,1,3,3,3-hexafluoro-propan-2-ol.

7) Process according to claim 4, wherein the concentration of the co-solvent ranges between 1 and 30%.

8) Process according to claim 1, wherein said reaction medium comprises a biphasic solution.

9) Process according to claim 8, wherein said reaction medium comprises an inert aprotic main solvent and a co-solvent having the capability of transferring the organic compound from one phase to the other.

10) Process according to claim 9, wherein the co-solvent is hexafluoroisopropanol.

11) Process according to claim 8, wherein said reaction medium includes a

first aqueous phase comprising the oxidizing agent and a second organic phase comprising the organic compound and a metalloporphyrin in an inert aprotic solvent.

12) Process according to claim 11, wherein said second phase comprises an inert aprotic main solvent and a co-solvent having the capability of transferring the oxidizing agent from one phase to the other.

13) Process according to claim 12, wherein said co-solvent is water-miscible.

14) Process according to claim 12, wherein said co-solvent is 1,1,1,3,3,3-hexafluoro-propan-2-ol.

15) Process according to claim 8, which comprises introducing a phase-transfer catalyst into the reaction medium, said phase-transfer catalyst having the capability of allowing the transfer of reactants from one phase to the other.

16) Process according to claim 15, wherein the phase-transfer catalyst is a tetraalkyl ammonium salt.

17) Process according to claim 16, wherein the tetraalkyl ammonium salt is dodecyl-trimethyl–ammonium bromide.

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Docket No.
A0000135-01-CFP

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PROCESS FOR CATALYZING THE OXIDATION OF ORGANIC COMPOUNDS

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ As United States Application No. _____ or PCT International Application Number _____
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Applications			Priority Not Claimed
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

60/148,079 (Application Serial No.)	**10 August 1999** (Filing Date)
60/150,101 (Application Serial No.)	**20 August 1999** (Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

PCT/EP00/07726 (Application Serial No.)	**09 August 2000** (Filing Date)	**pending** (Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORINEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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